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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/206,040	BYRUM ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The objection to the specification under 35 U.S.C. 132 is withdrawn. In addition to the evidence provided in the La Rosa declarations of 22 Sep. 2000 and 12 Jul. 2004, the Sequence Listing filed with the original application identifies LIB3049-003-Q1-E1-H7 as being the Clone ID for SEQ ID NO: 1.

Claim Rejections - 35 USC § 101

Claims 1 and 2 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, for the reasons of record set forth in the decision (pages 13-32) of Appeal No. 2002-0078 on Aug. 20, 2003 by the Board of Appeals under 37 CFR 1.196(b) and the Examiner's Answer of Aug. 6, 2001, as set forth in the Office action of 12 Jan. 2004 on pages 4-21.

Claim Rejections - 35 USC § 112 (Enablement)

Claims 1 and 2 remain also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, claim 1 contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention as directed to nucleic acid molecules comprising the EST of SEQ ID NO: 1, or its complete complement, and additional nucleotide sequences linked to the EST.

Claim Rejections - 35 USC § 112 (Written Description)

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 12 Jan 2004 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Arguments

Applicant's arguments filed 12 Jul. 2004 have been fully considered but they are not persuasive.

A) Response to Reply Section 2 (pp. 4-6).

Essentially the same arguments were presented in the Brief of 31 Jan. 2001 (Section 8.C), and addressed in the Examiner's Answer of 06 Aug. 2001 (pages 12,13, 15), with the pertinent arguments being repeated below.

Applicants assert that the claimed invention meets the utility and enablement requirements because they have proven that the claimed nucleic acid molecules can be used "to

identify the presence or absence of a polymorphism" and "as a hybridization probe for expression profiling".

The reply (footnote 1) states that the Examiner (Advisory Action of 11/22/00, page 12) conceded that the use "to identify the presence or absence of a polymorphism" had been proven. However, the only concession made by the Examiner on page 12 of the Advisory Action was that the Wiegand Declaration showed that a "polymorphism" could be detected between two species of plant – *Glycine max* and *G. soja*. However, as noted repeatedly the specification defines "polymorphism" as "a variation or difference in the sequence of the gene or its flanking regions that arises in some of the members of a species" (emphasis added). This information and utility involving *G. soja* was absent from the original disclosure (discussed in more detail below).

B) Response to Reply Section 2.A. (pp.6-9).

Essentially the same arguments were presented in the Brief of 31 Jan. 2001 (Section 8.C.1), except for discussion of the Concibido declaration, and were addressed in the Examiner's Answer of 06 Aug. 2001 (pages 16-18), with the pertinent arguments being repeated below.

The specification describes, in general, a variety of uses for nucleic acid molecules, like ESTs, that had been practiced in the art, such as the detection of a polymorphism. However, each specific nucleic acid molecule has specific uses that are very different from those for a different specific nucleic acid molecule. For example, an allele specific probe for determining the specific haplotype of a human HLA DR antigen cannot be used as a probe for detecting a specific polymorphism associated with the Bloom's disease locus or the cystic fibrosis disease locus. The specification generally teaches using the claimed polynucleotides to identify a

polymorphism, but does not teach that a polymorphism could in fact be detected, or a specific polymorphism that could be detected. The specification generally teaches using a polymorphism, detectable with the claimed nucleic acid molecules, as a molecular marker for a linked trait of interest, but does not teach either the polymorphism or the trait of interest. The court in *In re Kirk*, 153 USPQ 48, 53 (CCPA 1967) held:

> We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.

Similarly, the specification generally teaches using the claimed polynucleotide to measure the amount of mRNA in a tissue sample, such as in tissue profiling. However, except for the inference that the corresponding mRNA is present in at least one tissue of seeds in young soybean seed pods, the specification does not disclose any information on what other tissues express the corresponding mRNA, what level of expression occurs in these tissues, or whether the expression levels are regulated developmentally or in response to environmental conditions, or any scientific or practical significance for the expression. Significantly, the specification does not to teach any specific use for such information as it relates specifically to the claimed invention.

The Examiner had previously conceded the specification did disclose at least one other "fact" concerning the claimed nucleic acid molecules in addition to SEQ ID NO: 1 - young seeds pods (specifically the seeds) express the corresponding mRNA. However, the specification does not disclose any specific correspondence between these characteristics and any specific and

substantial use for the claimed nucleic acid molecule. For example, the specification does not identify even a single polymorphism *known*, by Applicants at the time the application was filed, to be detectable by the claimed nucleic acid molecules, or any relevance to the expression in young seeds.

Applicants appear to concede that the specification does not disclose any specific and substantial utilities that would require the complete structure of the corresponding mRNA and protein. As the reply (at page 8, 1st full para.) states:

> It is irrelevant whether the corresponding mRNA or polypeptide themselves have utility because Applicants are not relying on utility of the mRNA or polypeptide to establish utility of the claimed nucleic acid molecules.

The Wiegand Declaration does indeed show (¶s 22-23) that the claimed nucleic acid molecule can be used to detect a sequence difference between *Glycine max* and *Glycine soja*. However, the specification does not disclose such a use - in fact the specification does not mention *Glycine soja* at all. Therefore, at best all the Wiegand Declaration shows is a correspondence between the claimed invention and a possible specific utility disclosed in the Wiegand Declaration. In *Kirk*, the Petrow declaration had shown that some of the claimed compounds actually had a specific biological activity, however, this finding was not deemed dispositive by the Court because it is "what the compounds are *disclosed* to do that is determinative". As pointed out by the Board (page 24), the Wiegand declaration does not indicate that these results provide any significant knowledge, and therefore no evidence that such use constitutes a substantial utility.

The Concibido declaration under 37 CFR 1.132 filed 12 July 2004 is insufficient to overcome the rejection of claims 1-2 based upon a lack of utility as set forth in the last Office

action. The declaration refers to a resume (Exhibit A) in ¶ 1; this exhibit was not received by the Office. Declarant (¶ 3) asserts that the claimed sequence could be used to detect polymorphisms in *Glycine max* and *Glycine soja*, and that such use would be well known to a person of ordinary skill in the art. However, the specification does not disclose such a use, and does not mention *G. soja* at all. The sequence differences between *G. max* and *G. soja* reported in the Wiegand declaration are not "polymorphisms" as that term has been defined in the specification. No evidence or explanation has been provided that this use "would be well known;" the statement is opinion not fact. Also, it is irrelevant whether such use would be well known at the time the declaration was made since it is uses that were well known at the time the application was filed that are at issue here. Even if such a use was well known at the time the application was filed, the Declarant provides no evidence indicating such use would be substantial, i.e. providing benefit to the public in a "real world" context, as opposed to a use directed to satisfying scientific curiosity about the claimed nucleic acid molecule.

Declarant states (¶ 4) that varieties of *G. max* are more closely related to each other than *G. max* is to *G. soja*, and that the frequency of polymorphisms between varieties of *G. max* is lower than between *G. max* and *G. soja*. Declarant concludes that the experiments described in the Wiegand declaration demonstrate that the claimed nucleic acid molecule could be used to screen for the presence and absence of polymorphisms between varieties of *G. max*. However, the Wiegand declaration does not demonstrate using the claimed nucleic acid molecule to detect the presence or absence of polymorphisms in *G. max*. It is conceded that if there are restriction fragment length polymorphisms in *G. max* that could be detected by hybridization with SEQ ID NO: 1, then the methods such as described in the Wiegand declaration could be used for that

purpose. (It is not conceded, however, that such methods could be used to detect sequence polymorphisms that do not alter a restriction endonucleases recognition sequence.) However, as has been repeatedly explained, such a use is not a substantial utility. The specification does not disclose a single use for the claimed nucleic acid molecule in a utility that includes detecting a polymorphism if there is no polymorphism to detect among *G. max* varieties. The process of using the claimed invention to determine whether there is a polymorphism to detect is nothing more than using the claimed invention to determine whether it has utility in detecting polymorphisms. Such a use does not meet the statutory utility requirement, i.e. it is "use testing".

C) Response to Reply Section 2.A.1 (pp.9-10) & 2.A.4 (pp. 24-25).

Essentially the same arguments were presented in the Brief of 31 Jan. 2001 (Section 8.C.1, last paragraph and 8.C.1.a), and were addressed in the Examiner's Answer of 06 Aug. 2001 (pages 18-26), with the pertinent arguments being repeated below.

Applicants argue that the claimed nucleic acid molecules have utility as a "tool" useful to "locate and measure nucleic molecules such as mRNA or chromosomal DNA that hybridize to SEQ ID No. 1 or its complement". The reply does not indicate any source for the hypothetical nucleic acid molecules described, but based on the specification, it is presumed that these hypothetical nucleic acid molecules are to be found in *G. max* or other plant species. The argument in the reply compares the claimed invention to a microscope, a gas chromatograph, or an unspecified screening assay.

A microscope is useful for determining structure of *any* sample of interest at the macroscopic, microscopic or molecular level, depending on the type of microscope. It is a generally useful tool for a wide range of specific uses. One does not usually use a microscope to

study related microscopes. In contrast, Applicants argue that the claimed nucleic acid molecules are useful to detect or measure nucleic acid molecules that possess a certain level of structural relatedness to the claimed nucleic acid molecules, the level of relatedness being defined by hybridization to the claimed nucleic acid molecules. However, the only such nucleic acid molecule that is disclosed in the specification is one that consists of or comprises SEQ ID No. 1 or its complement; the specification discloses *no* nucleic acid molecule that hybridizes with the claimed nucleic acid molecules that does *not* consist of or comprise SEQ ID No. 1 or its complement, and presumably in the genome of *G. max*. The Wiegand declaration shows that the closely related species *G. soja* contains nucleic acid that will hybridize with SEQ ID NO: 1, but the specification does not disclose this specific use. Neither the specification nor the Wiegand declaration indicates how this cross-species hybridization provides a specific and substantial utility. All arguments pertaining to the utility of the claimed invention with respect to studying the corresponding genomic DNA and mRNA found in *G. max*, would also apply to any homologous nucleic acid molecules found in other plant species, such as *G. soja*. In so much as the specification does not describe a specific and substantial utility for the corresponding nucleic acids in *G. max*, so does it fail to describe a specific and substantial utility for the corresponding nucleic acids in other plant species. Applicants do not explain how locating and measuring mRNA or chromosomal DNA that hybridizes with SEQ ID NO: 1 goes beyond simple characterization of the claimed nucleic acid molecule and exploring what it might be used for, Such uses are not sufficient to satisfy §101. See *Brenner v. Manson*, 148 UDSP 689 (US 1966) at pages 695-696.

The reply states that the specification teaches introducing the claimed nucleic acid molecules into a plant or plant cell as an antisense or sense inhibitor, and then using the plant or plant cell for screening compounds as herbicides. However, the specification does not disclose such a utility. The specification (page 64, line 19 to page 65, line 22) teaches that the claimed invention can be used to encode a sense or antisense inhibitor. However, the specification does not show that the claimed invention can be used either as a sense or antisense inhibitor or in screening compounds as herbicides. Additionally, the specification does not teach any consequence that would result from such inhibition, or how such inhibition would be useful in a "real world" context. Therefore, claimed invention has no *immediate* use in this context other than as an object of further scientific investigation in order to first confirm whether the claimed nucleic acid molecule can in fact be used as a sense or antisense inhibitor, what effect on the plant such inhibition would have, and to then determine a "real world" use for such inhibition, if inhibition can be achieved. Thus, the specification provides no specific and substantial utility for the claimed invention as a sense or antisense inhibitor. This utility is neither specific nor substantial because the specification does not disclose: 1) that it had been carried out; 2) what inhibition to measure or how to measure it; 3) what result would have been obtained if it had been carried out; or 4) what practical benefit would have arisen by using the claimed invention in this manner. For all of these reasons, Applicants' arguments equating this speculative screen to some nebulous "cell-based assay" are therefore unpersuasive.

The reply asserts that using the claimed nucleic acid molecule for expression profiling meets the statutory utility requirement. The specification does not discuss expression profiling *per se*. It does teach (pages 12, line 20 to page 13, line 16; page 36, line 19 to page 40, line 6)

using the claimed nucleic acid molecules to determine whether an mRNA, and by inference a protein, that corresponds to the claimed nucleic acid molecule is present in a particular cell or tissue. Since the nucleic acid of SEQ ID NO: 1 was obtained from young soybean seeds in young seed pods, it can be inferred that at least one tissue present in young seeds expresses an mRNA corresponding to the claimed nucleic acid molecule. The specification generally describes various methods known in the art for detecting mRNA in biological samples.

However, the specification does not disclose any practical reason for doing so, or any *immediate* benefit that the public may derive from doing so. The specification does not disclose which of the different tissues or cells present in the young seeds express the corresponding mRNA. The specification does not disclose what other cells and tissues of a soybean plant express or do not express the corresponding mRNA. The specification discloses no environmental conditions that would increase or decrease expression of the corresponding mRNA. Nor does the specification disclose any phenotype or trait that would be conferred on a plant, tissue, or cell as a result of overexpression or underexpression of the corresponding gene relative to wild-type expression levels, or as a result of expression of the corresponding gene at inappropriate times during plant development or in inappropriate tissues or cells in a plant. While the claimed invention could be used to provide such information, until such information is known, one skilled in the art can only guess at the result and can only guess at what practical benefit or specific and substantial utility may arise from such information. Therefore, the only readily apparent utility for obtaining such information is to aid in elucidating the biological function of the corresponding gene and its expression products. As such, this disclosed utility is directed at using the claimed invention in order to characterize itself, perhaps with the hope that

the information may suggest a practical utility to one skilled in the art. Thus, Applicants' argument that monitoring expression of the mRNA satisfies §101 is not persuasive.

The Wiegand Declaration shows that the claimed nucleic acid molecule can be used to detect a specific mRNA or for measuring the amount of mRNA in a sample, but the specification does not disclose any practical benefit, i.e. a substantial utility, for doing so. Any *bona fide* EST can be used to detect the mRNA from which it was made and measure the amount of such mRNA in various samples, such as tissue. However, unless some biological or physiological significance can be attached to the expression pattern or level, it is unclear what practical benefit would be obtained in the absence of information on the significance. The specification does not disclose any "real world" significance either to the expression pattern or the expression level of the corresponding mRNA in any plant cell or tissue. The specification does not disclose what tissues normally express the corresponding mRNA (other than young seeds) or at what levels (in any tissue, including young seeds); nor does it disclose what environmental stimuli affect the levels of mRNA expression or how the expression levels change in response to any one stimulus. For example, if young seed pods of a particular soybean variety were found to contain elevated levels of the corresponding mRNA when grown in the field as compared to being grown in a greenhouse, would that mean that the field-grown plant was suffering - or benefiting - from the field growth conditions. If the field-grown plants were suffering, would it be from drought-stress, over watering, too much light, too little light, or something else? Applicants assert in footnote 5 that using the claimed nucleic acid molecules to characterize the expression of the corresponding mRNA is in a "real world" context. The Examiner disagrees.

First, since the SEQ ID NO: 1 is a partial sequence, i.e. an EST, of a cDNA that is presumed to be a faithful copy of part of an mRNA existing in young seeds, SEQ ID NO: 1 is then presumed to be a partial sequence of that corresponding mRNA. Consequently, that corresponding mRNA *is* a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1 or its complement, and the part of the mRNA that is identical to SEQ ID NO: 1 *is* a nucleic acid molecule consisting of SEQ ID NO: 1 or its complement. Therefore, the use of the claimed nucleic acid molecules in assays to determine which plant tissues contain the corresponding mRNA and in what amounts, or in assays to determine the levels of the corresponding mRNA in response to environmental stimuli is clearly using the claimed invention as an object of scientific investigation in order to determine this information about the claimed nucleic acid molecules themselves.

Furthermore, the specification does not disclose any specific information about the expression pattern or level of the corresponding mRNA in different tissues or relating the expression to any trait of interest, nor does it describe how this missing information could be put to a specific use in obtaining a practical benefit. Consequently, one skilled in the art would first be required to determine the tissue distribution of the corresponding mRNA or to determine the level of expression of the mRNA in response to environmental stimuli. Then, one skilled in the art would have to develop a practical use for the information determined. Thus, the specification simply invites one skilled in the art to experiment on the claimed nucleic acid molecules with respect to detecting and measuring the corresponding mRNA in order to determine practical applications based upon the results obtained.

Footnote 6 asserts that the claimed nucleic acid molecules can be used to determine the location of the corresponding genomic DNA sequences on a physical or genetic map without knowing anything more than SEQ ID NO: 1. The footnote merely summarizes what is stated at pages 11-12 of Applicants' response of 22 Aug. 2000 (which does not reference any articles) and in the Wiegand Declaration.

First, contrary to Applicants' assertion, it is not possible to determine the location of the corresponding genomic DNA sequences on a genetic map without knowing anything more than SEQ ID NO: 1. The placement of any locus on a genetic map requires that the locus be defined by two or more alleles that can be followed after meiosis (sexual reproduction) with respect to alleles of one or more other loci. Alleles of a locus can be distinguished from each other based on physical differences, e.g. sequence polymorphisms, in the genomic DNA (i.e. genotype), and/or based on phenotypic differences. The specification discloses no phenotypes associated with the claimed nucleic acid molecules nor does it disclose any physical differences in the corresponding genomic DNAs of various *G. max* isolates that can be detected with the claimed nucleic acid molecules. Applicants has repeatedly failed to explain how one skilled in the art can be expected to determine a genetic map location for the corresponding genomic DNA sequence knowing only SEQ ID NO: 1. Also, the specification does not disclose a physical map location for genomic DNA corresponding to SEQ ID NO: 1, nor does it disclose how knowing the physical map location of the corresponding genomic DNA can be put to any *immediate* practical purpose.

Second, using the claimed nucleic acid molecules to determine the location of the corresponding genomic DNA sequences on a physical map (or on a genetic map), constitutes

investigation on the claimed invention to determine what chromosomal location can be detected using the claimed nucleic acid molecules. Until the chromosomal location corresponding to the claimed nucleic acid molecules is known, one skilled in the art cannot use the claimed invention to study any other chromosomal locus, gene, or trait that may be linked to the corresponding chromosomal location. The specification does not identify any chromosomal locus, gene, or trait that is linked to the chromosomal location corresponding to the claimed nucleic acid molecules, and thus does not identify any chromosomal locus, gene, or trait for which the claimed nucleic acid molecules may be used in the capacity of a molecular marker, as asserted.

Simply because those skilled in the art have used other *characterized* molecular markers for defined traits or characteristics in genetic mapping (of linked loci), marker-assisted breeding, transgenic crop production, crop monitoring diagnostics, gene identification (presumably of other genes), etc., does not mean that the claimed nucleic acid molecules can necessarily be used for any or all of these purposes. Using the claimed nucleic acid molecules in the capacity of a probe for a molecular marker, e.g. a polymorphism, is simply a speculative use for the claimed nucleic acid molecules that would require experimentation in order to determine a specific and substantial use, if any, for the claimed nucleic acid molecule, such as being a molecular marker for some particular trait of interest, e.g. drought tolerance.

D) Response to Reply Section 2.A.2. (pp. 10-11).

Applicants assert that they have proved the claimed nucleic molecules may and have been used to detect a polymorphism in a "population" of soybean plants, citing the Wiegand declaration at paras. 22-23 and the Concibido declaration at ¶ 4. However, nothing in the Wiegand declaration refers to detecting polymorphisms in a "population" of soybean plants.

Rather, paras. 22-23 relate to sequence differences between two separate species, which as disclosed in Ahmad (J. Hered. 70: 358-364, 1979, at page 363-364) evolved in the same geographic location, i.e. in nature, *G. max* and *G. soja* are genetically isolated from each other, and cannot be described as being part of a population. Also, the genetic differences between these species are not polymorphisms, as defined in the specification. The content of the Concibido declaration has been addressed above in the response to section 2.A.

E) Response to Reply Section 2.A.2.a. & 2.A.2.b. (pp. 12-15)

Essentially the same arguments were presented in the Brief of 31 Jan. 2001 (Section 8.C.1, last paragraph and 8.C.1.b), except for discussion of the Concibido declaration, and were addressed in the Examiner's Answer of 06 Aug. 2001 (pages 26-36), with the pertinent arguments being repeated below.

Applicants' arguments are directed to the use of the claimed nucleic acid molecules as probes to detect polymorphisms. It is asserted that the final Office action "provides no support (legal or factual) for the proposition that before detection of polymorphisms can be recognized as a legal utility, actual polymorphisms must be shown to exist". The specification (page 28, full ¶ 4) defines "polymorphism" as "a variation or difference in the sequence of the gene or its flanking regions that arises in some members of a species" (emphasis added). The specification from page 29 through page 35, line 3 discusses various types of sequence polymorphisms and how they are detected. The specification describes two general uses of sequence polymorphisms which can be detected with a nucleic acid molecule, such as the claimed nucleic acid molecule, used as a hybridization probe. First, a polymorphism serves as a molecular marker for a mutation that affects the expression of a product encoded, at least in part, by the nucleic acid

molecule, i.e. the mRNA or protein corresponding to the nucleic acid molecule. The polymorphism can then be used to determine whether a particular phenotype is conferred by the mutation, e.g. by linkage analysis of the polymorphism relative to the phenotype. If the mutation is found to confer a phenotype, then the polymorphism serves as a molecular marker for both the phenotype and the mutation (specification, page 27, line 9 through page 28, line 6). Second, the polymorphism serves as a molecular marker for desirable traits that are genetically linked to the polymorphism, i.e. traits that are conferred by genes located on a chromosome very near the genomic location corresponding to the nucleic acid molecule (specification, page 35).

These uses for a nucleic acid molecule, which like the claimed nucleic acid molecule is an EST, are general in the sense that any EST has potential use as a probe to detect a polymorphism, but only IF such a polymorphism exists. To determine whether a polymorphism exists at a specific chromosomal location requires hybridization to at least two individual chromosomes, and generally involves analyzing genomic DNA from multiple members of a species; the specification discloses no such analysis. The specification does not disclose: 1) whether the claimed nucleic acid molecule can in fact detect a polymorphism, or even whether such a polymorphism exists; and 2) at least one specific example of at least one of the types of polymorphisms described in the specification (pages 29-35). There is also no evidence of record that polymorphisms detectable by the claimed nucleic acid molecule were known to exist prior to Applicants' filing date. The specification does not disclose any utility in this context for a nucleic acid molecule or EST that cannot detect a polymorphism. Therefore, using the claimed invention to first determine whether or not the claimed nucleic acid molecule can, in fact, detect a polymorphism *is* to determine whether or not the claimed invention has a utility that requires

detecting a polymorphism, i.e. it is "use testing" and not substantial. Since the specification does not identify even one specific polymorphism that can be detected with the claimed nucleic acid molecule, the specification does not show any specific correspondence between the disclosed general utility and the claimed subject matter, regardless of any specific application requiring detection of polymorphisms.

Furthermore, these uses for a nucleic acid molecule are general in the sense that any gene corresponding to an EST has the potential to confer a detectable phenotype if mutated or has the potential to be genetically linked to a desirable trait. Thus, any polymorphism that can be detected with a nucleic acid molecule has the potential to serve as a marker for such a mutation or phenotype. However, the specification does not disclose that the gene corresponding to the claimed nucleic acid molecule is mutated in any soybean cultivars or that such a mutation confers any phenotype (useful or not) or that making such a mutation would confer any particular phenotype. The specification also does not disclose any desirable trait that is closely linked to a polymorphism that could be detected with the claimed nucleic acid molecule. Since the specification does not identify even one such mutation or desired phenotype that can be "marked" by a polymorphism detected with the claimed nucleic acid molecule, the specification does not show any specific correspondence between the disclosed general uses and the claimed subject matter. The process of identifying any hypothetical mutation in the corresponding gene and then identifying any phenotype conferred by the mutation, or the process of identifying any desired phenotype that could be "marked" by the polymorphism *is* solely a process of identifying a use for the claimed nucleic acid in this context, i.e. such use is not substantial.

The claimed invention is compared to a gas chromatograph. However, the logical basis for this analogy is unclear. Gas chromatographs are used to analyze any chemical compound, known or unknown, that can be put into the gaseous state. Those skilled in the art use gas chromatographs to analyze both known and unknown compounds. When the compound is unknown, the results obtained are compared to results for known compounds, e.g. standards. Applicants compare the failure to detect a polymorphism with the claimed nucleic acid molecules, to the failure to detect a specific known compound in a sample, e.g. chlorine in an oil sample. This analogy fails to address Applicants' own definition of the term "polymorphism". The specification (page 28, full ¶ 4) defines "polymorphism" as "a variation or difference in the sequence of the gene or its flanking regions that arises in some members of a species." It follows from this definition that if there is no "variation or difference in the sequence of the gene or its flanking regions" among "members of a species", then no polymorphism exists, i.e. a polymorphism is absent, in this region of the genome. A "polymorphism" is a collective concept defined by at least two variants (or alleles) found within members of a species collectively. Thus, one detects the *presence* of a polymorphism by analyzing multiple members of the species, i.e. analyzing a population. While one can detect the absence (or presence) of a specific allele of the polymorphism in a specific individual member of the species, one cannot detect the *absence* of a polymorphism *per se* based on one individual alone. The absence of a particular allele necessarily means that a different allele is present. The specification does not disclose a specific and substantial utility for the claimed invention in the capacity of detecting polymorphisms, because it does not disclose whether in fact any polymorphism exists in *G. max* to be detected by the claimed nucleic acid molecule. Thus, the specification leaves open the possibility that there

may be no polymorphism to detect. The specification does not teach any polymorphism or any significance for a hypothetical polymorphism. Consequently, the activity for determining whether such polymorphisms exist is neither specific nor substantial. With respect to the gas chromatograph analogy, one can only detect the absence of a compound, such as chlorine, in a sample, *if* it was already known that chlorine could, in fact, be detected by the gas chromatograph were it present in the sample.

Applicants argue that this use for the claimed invention is not use testing "because it determines information about the plant and its genetic traits, not additional information about the claimed nucleic acid sequence". However, the specification does not disclose any such "information about the plant and its genetic traits". Rather, the specification describes in very general terms the uses to which other, presumably prior art, nucleic acid molecules have been put in order to "determine information about the plant and its genetic traits". Consequently, it is left wholly for one skilled in the art to determine whether or not the claimed nucleic acid molecules can, in fact, be used to identify a polymorphism, which is use testing. Then, if a polymorphism can be detected, it is left wholly for one skilled in the art to determine if, in fact, the polymorphism can be used as a molecular marker for at least one phenotypic trait of interest, and if so, which one. This also is use testing.

Applicants assert that the credibility of this utility was challenged in final Office action at page 10. However, the final Office action did *not* challenge the credibility, i.e. operability, of identifying polymorphisms. In footnote 8, Appellant argues that "the use of the claimed nucleic acid molecules to identify the presence or absence of polymorphisms is a use of the claimed nucleic acid molecules, not a preparatory step for another use". However this "use" is *not* a

specific and substantial use as required under 35 USC 101. For the reasons set forth in the rejection, the specification does not disclose any utility in this context for a nucleic acid molecule or EST that does not detect a polymorphism because no polymorphism exists. Therefore, using the claimed invention to first determine whether or not a polymorphism exists to be detected by the claimed nucleic acid molecule *is* to determine whether or not the claimed invention has even potential utility in a method that requires detecting a polymorphism. It is therefore a non-statutory use that is a preparatory step for identifying a specific and substantial use, i.e. it is "use testing"; and the fact situation in *Kirk* clearly applies. If Applicants' argument were applied to the fact situation in *Kirk*, it would have been argued that using the claimed steroids to identify their biological activity would be a use of the claimed steroids, "not a preparatory step for another use", such as using the claimed steroids consonant with the biological activity identified.

With respect to comparing this utility to that of a "cell-based screening assay", Applicants assert that the Examiner implied that a diagnostic test such as ELISA has no utility because it does not identify useful ligands. However, Applicants' argument raised on pages 8-9 of the after-final response of 22 Aug. 2000 (answered in the Advisory action in the paragraphs bridging pages 8-9) compared using the claimed invention to that of a cell-based assay "used to screen for desired compounds" such as ligands that bind to a receptor involved in a biological process. Such an assay is not comparable to an ELISA diagnostic assay (which is an antibody-based assay, not a cell-based assay) aimed at detecting a compound, such as detecting an antigen from a pathogenic bacterium in a blood sample. Page 11 of the Advisory action responds to a separate argument raised in the after-final reply at page 10, where identifying polymorphisms using the claimed invention was compared to "a biological screen for chemicals which

themselves might not have legal utility"; arguing that the assay itself and products used therein would still have utility. No more details concerning this hypothetical assay were mentioned, specifically no allusion was made to a diagnostic assay such as ELISA; nor was any legal basis provided on utility. It was this latter hypothetical assay that was compared to *Brenner*, since it had been assumed that the goal of the method was the "chemicals" identified, not the information provided by the assay, such as would be the case in a diagnostic assay. The Examiner stands by the rebuttal to Applicants' original argument regarding assays designed to identify "desired compounds" that themselves have no known utility.

Applicants compare "identifying the presence or absence of a polymorphism" for determining whether two organisms share a genetic heritage to an ELISA diagnostic assay. This analogy is similar to that of the gas chromatograph discussed above, and the same response applies to this analogy. The claimed invention cannot have any use in this capacity unless it was already known that there was a polymorphism to detect and that some specific and substantial use was known for the detecting the polymorphism. However, the specification does not disclose that there was, in fact, any polymorphism in the corresponding *G. max* genome, or genome of any other plant species, that could be detected with the claimed invention, much less whether the polymorphism was linked to any desired or undesired trait for which such a polymorphism would be a marker.

Finally, Applicants state that these issues "are beside the point because the claimed nucleic acid molecules did identify a polymorphism", referring to the results presented in the Wiegand Declaration (paras. 20, 23). However, these issues are not "beside the point" because the specification left the question open as to whether a polymorphism could, in fact, be detected

and did not identify any polymorphism that could be detected. In *Kirk* at page 52, the Petrow declaration had shown that some of the claimed compounds actually had a specific biological activity, however, this finding was not deemed dispositive by the court because it is "what the compounds are *disclosed* to do that is determinative". As with the Petrow declaration in *Kirk*, the Wiegand Declaration (paras. 20-23) is not dispositive here in showing a potential use that is not disclosed in the specification.

Furthermore with respect to the Wiegand Declaration, the specification does not define a "polymorphism" in the context of sequence variation between species, such as between *Glycine max* (soybean) and *Glycine soja* (wild soybean), nor does the specification teach any utility for detecting sequence variation between species of the genus *Glycine*. (In fact the specification does not even mention *Glycine soja* or any other species of *Glycine*.) The reply asserts that it is not true that *G. max* and *G. soja* are different species because they can interbreed to produce fertile offspring, citing a definition obtained from "Oxford Dictionary of Biochemistry and Molecular Biology" (footnote 11). However, the cited reference has not been provided and cannot be evaluated in this context. In taxonomy, the capitalized first term, e.g. *Glycine*, is the genus name for an organism and the second term, e.g. *max*, is the species name for an organism. The fact that *G. max* and *G. soja* have been given different species names means that they are considered by those skilled in the art, particularly in *Glycine* taxonomy, to be separate species. According to the U.S. National Center for Biotechnology Information, these two plants are currently considered to be separate species of the genus *Glycine* (see Taxonomy Browser on the World Wide Web at ncbi.nlm.nih.gov/htbin-post/Taxonomy). Furthermore, Ahmad et al. discloses that "Chromosomal differentiation together with wide genetical and morphological

differences provide evidence that *G. max* and *G. soja* are two distinctly separate species" (p. 363, col. 2), despite the fact that they can be interbred. Thus, those skilled in the plant taxonomy art, had considered and still consider these two plants to be separate species. Therefore, the example provided in the Wiegand Declaration of detecting sequence variation between species of a genus, *G. max* and *G. soja*, is not a utility disclosed in the specification. Polymorphism is defined in the specification in the context as among members of a species, not between species of a biological genus. Rather the Wiegand Declaration is an attempt to add subject matter to the specification for which there is no support in the original application.

In addition, the Wiegand Declaration (¶ 22) states that "twenty restriction digests" of chromosomal DNA from *G. max* and *G. soja* were examined. (As noted above, the observed "polymorphism" between *G. max* and *G. soja* does not meet the definition for polymorphism set forth in the specification.) The "twenty restriction digests" are presumed to mean chromosomal DNA digested with each of twenty different restriction endonucleases. A sequence difference could be detected in four of the twenty digests. The results shown in Exhibit C of the declaration presumably show the results for these four digests, and for one (*Hin*dIII) of the sixteen digests in which no evidence of sequence difference could be detected. This experiment is a good example of "use testing" - to determine which, if any, of the twenty restriction digests the claimed nucleic acid molecules could be used to detect a sequence difference between these two *Glycine* species. The declaration shows that the claimed nucleic acid molecules have *no* use for detecting a sequence difference in 80% (16 of 20) of the digests. This information is not disclosed in the specification. Applicants' argument side-steps the issue. The determinative issue is what properties the instant specification discloses for the claimed nucleic acid molecules, not what

properties were later discovered, e.g. by Dr. Wiegand. As an analogy to the opinion of the Court in *Kirk* (at page 52), while the declaration may show that the claimed nucleic acid molecules do *in fact* detect sequence differences between *G. max* and *G. soja* in four of twenty restriction digests, the original specification as filed did not disclose any such use.

Applicants refer to ¶ 3 of the Concibido declaration, the content of which has been addressed above in the response to section 2.A.

F) Response to Reply Section 2.A.2.c. (pp. 15-16)

Applicants assert that the Office has acknowledged that the tests performed by Dr. Wiegand detected the presence of a polymorphism between *G. max* and *G. soja*. This assertion is misleading. The examiner has acknowledged that the Wiegand declaration shows that *G. max* and *G. soja* contain nucleic acid that hybridizes to SEQ ID NO: 1, and that there are sequence differences between the two. The Examiner has repeatedly pointed out that these sequence differences are not polymorphisms, as "polymorphism" has been defined. The Board did not address this issue for the reasons given on page 24 (footnote 7) of its decision of 20 Aug. 2003.

Applicants acknowledge that the specification defines "polymorphism" as "a variation or difference in the sequence of the gene or its flanking regions that arises in some members of a species," and then imply that because *G. max* and *G. soja* are able to interbreed and produce fertile offspring that they describe a single species. Applicants base this argument on alleged definitions found in two references, which have yet to be supplied to the Office. "Argument of counsel cannot take the place of evidence lacking in the record." *In re Scarbrough*, 182 USPQ 298, 302 (CCPA 1974). In contrast, the Office has provided evidence that the US National Center for Biotechnology Information consider these to be separate species, and Ahmad provides

reasons why these are considered separate species by those of skill in this art. The Office has not ignored evidence of sequence differences between these two species, as implied by Applicants. Instead, the Office and Board have repeatedly addressed its relevance to the issue of whether the utility requirement has been met, and explained why such evidence does not advance Applicants' cause.

Applicants assert that the claimed nucleic acid molecules will, in fact, detect the "presence or absence" of polymorphisms between *G. max* varieties, citing the 2nd La Rosa Decl. at ¶ 8 and the Concibido Decl. at ¶ 4. The sufficiency of the latter has been addressed above in section B. The La Rosa declaration simply repeats the assertion. However, this assertion applies to the operability (and credibility) of the using the claimed nucleic acid molecules to hybridize to nucleic acid from *G. max*, and the credibility of the asserted general uses has not been addressed in the rejection. It is not germane to the issue of whether the claimed nucleic acid molecule has a specific and substantial utility. The suggestion that one determine whether there is or is not a polymorphism associated with the genetic locus in the *G. max* genome corresponding to SEQ ID NO: 1 is simply an invitation to experiment in order to further characterize the invention and to determine whether the claimed invention can be used to detect polymorphisms for some further purpose. If such a polymorphism exists, which Applicants have yet to demonstrate, then one may develop a substantial use for detecting it. Conversely, if no such polymorphism exists, then the claimed invention has no use in any substantial utility that involves the detection of polymorphisms, e.g. perhaps as a marker for a desirable trait. This type of exploratory use is a not specific utility because any EST from any organism has the same use, and is not substantial because there is no *immediate* benefit to the public arising from such use.

G) Response to Reply Section 2.A.2.d. (pp. 16-17).

The issue of whether the probe composition described in paragraphs 14-17 of the Wiegand declaration was relevant to the use of a polynucleotide comprising or consisting of SEQ ID NO: 1 was raised by the Board in its decision (e.g. at pages 23-24). In reviewing ¶ 16, the Examiner concurs with ¶ 7 of the 2nd La Rosa declaration. The "probe" described in the Wiegand Decl. at ¶ 16 is a mixture of nucleic acid molecules. Most of which differ in sequence from SEQ ID NO: 1 by several nucleotides and probably some of which are embraced by SEQ ID NO: 1. While using such a probe mixture might be expected to result in slightly higher non-specific hybridization (background noise) than would result from using molecules defined by SEQ ID NO: 1 itself, one would not expect specific hybridization (the desired hybridization) to be impaired. One of skill in this art would expect very similar results using a nucleic acid molecule defined by SEQ ID NO: 1 itself as those obtained with the probe described in the Wiegand declaration.

H) Response to Reply Section 2.A.2.e. (pp. 17-20).

Applicants reiterate their arguments in the Reply of 06 Oct. 2003 (pages 4-6) concerning the Board's discussion of a "utility spectrum" in their decision of 20 Aug. 2003. No further response by the Examiner than was presented in the Office action of 12 Jan. 2003 (pages 31-32) is deemed necessary.

I) Response to Reply Section 2.A.3. (pp. 20-24).

Essentially the same arguments were presented in the Brief of 31 Jan. 2001 (Section 8.C.1.c), and were addressed in the Examiner's Answer of 06 Aug. 2001 (pages 36-41), with the pertinent arguments being repeated below.

The reply asserts that the claimed nucleic acid molecules have use as probes for other molecules or as a source or primers. The specification (page 24) teaches that the claimed nucleic acid molecules can be used to isolate nucleic acid molecules from other plant species, such as nucleic acids that encode a homologue of the polypeptide corresponding to the claimed nucleic acid molecule. However, the specification does not disclose any such nucleic acid molecules from other plant species. Nor does the specification teach what use these nucleic acid molecules of other plant species would have. Any uncharacterized nucleic acid molecule from a species of organism can be used in this manner, thus such a utility is not specific to the claimed invention, and since the specification discloses no biological function or any use for any gene corresponding to the claimed nucleic acid molecule, any such nucleic acid molecules of other plant species would also lack substantial utility - the artisan would first have to experiment to determine a specific, substantial and credible use for any such nucleic acid molecules isolated.

The specification (pages 25-27) also teaches that the claimed nucleic acid molecule would have utility for initiating a chromosomal walk in order to isolate transcriptional regulatory sequences and promoters, including those of the gene corresponding to the claimed nucleic acid molecule. The specification (page 26, lines 6-8) teaches that the "ESTs isolated from the library of the present invention are used to isolate promoters of tissue-enhanced, tissue-specific, developmentally- or environmentally-regulated expression profiles" (not simply a promoter active in young seed pods). The specification draws on the prior art to teach how promoters may be identified. Significantly, the specification does not disclose any promoters at all, much less a promoter corresponding to the claimed nucleic acid molecule. Furthermore, the specification does not disclose whether expression of the gene corresponding to SEQ ID NO: 1, or any other

gene within "chromosome walking" distance of the corresponding gene is tissue-enhanced, tissue-specific, developmentally- or environmentally-regulated. The fact that the corresponding gene is expressed in young seeds does not indicate how the expression of the gene is regulated. The Wiegand Declaration (¶ 17) discloses that the corresponding gene is also expressed in young sprouts and adult leaf at roughly the same level. However, there is no evidence that expression of the corresponding gene is either tissue-enhanced or tissue-specific. Further, there is no evidence of record to indicate whether or not its expression is developmentally- or environmentally-regulated expression. More importantly, the original disclosure contains no such information.

Also, using a nucleic acid molecule, such as an EST, as a starting point for a chromosome walk in an effort to isolate a promoter is a general characteristic common to nucleic acid molecules isolated from any organism. This is a utility not specific to the claimed polynucleotide. Furthermore, since the specification does not disclose any specific promoter, either from the corresponding gene or from a gene linked to the corresponding gene, the specification lacks any specific correspondence between the claimed nucleic acid and any specific product, i.e. promoter, that could be made using it. The specification does not provide for a specific utility for the claimed nucleic acid molecules in this capacity as an intermediate to obtain a theoretically useful product simply because it does not disclose or describe any specific useful product that could be made. Rather, the specification merely directs one skilled in the art to use the claimed invention to go out and hunt for such a promoter, and after characterizing that promoter, determine what specifically to use it for. Thus, Applicants' argument is not persuasive.

While the specification teaches (page 24, ¶ 3) that the claimed nucleic acid molecules "*may be employed* to obtain other nucleic acid molecules" (emphasis added), the specification does not indicate that any such nucleic acid molecules *had been* obtained, nor does it describe any characteristics possessed by such nucleic acid molecules. As to whether such molecules could, in fact, be obtained, the Office can neither prove nor disprove the assertion because the Office does not have laboratory facilities. At the time the application had been filed, future experimentation on the part of one skilled in the art would have been required to determine which, if any, other plant species contained nucleic acid molecules that could have been obtained using the claimed invention, and under what experimental conditions. An example of such undisclosed, future experimentation is shown in the Wiegand declaration (¶ 22).

In this context, the claimed invention does not compare to a golf club, because one knows what a golf ball is and how to use the golf club to hit it, whereas the specification does not disclose or describe with particularity any known useful nucleic acid molecule that can be obtained, such as the corresponding promoter - it simply invites the skilled artisan to provide such information by further experimentation.

Even assuming, *arguendo,* that the corresponding promoter exists there is no more guidance for its isolation, and eventual use, than knowing that a haystack contains a needle - at least one is presumed to know what the needle looks like. Also, the specification does not disclose the distance or direction one has to walk on a chromosome from the corresponding location to reach the corresponding promoter. Thus, starting the walk at the corresponding chromosomal location is no more help in identifying the promoter than is picking a specific location in a haystack to start looking for a needle when one does not know where the needle is

relative to the starting location. Initiation of a chromosome walk at the corresponding chromosomal location is considered non-specific because any EST would serve the purpose for isolating an uncharacterized promoter, since any chromosomal location is expected to be physically linked to a promoter, although neither its structure or its distance from the starting location would be known. The Examiner agrees that not just any EST would serve in isolating the promoter corresponding to the claimed nucleic acid molecules, but since the specification asserts only that the promoter exists, this agreement is moot. As to whether one skilled in the art may be able to eventually identify and isolate the corresponding promoter, this is irrelevant, particularly since the corresponding promoter was and is unknown. The specification does not disclose sufficient characteristics of the corresponding promoter, such as its sequence or precise location (or even direction) relative to the genomic location corresponding to the claimed nucleic acid molecule, to inform one of what the corresponding promoter is or when it has been isolated. For example, a nucleotide sequence is identified during the chromosome walk as a putative promoter by sequence analysis, is then subcloned into operable linkage with a reporter gene and transfected in into young soybean seed cells, but found not to express the reporter gene in the cells. This result could mean the putative promoter: is not truly a promoter, i.e., a false positive; is not the corresponding promoter; or is incomplete, i.e., lacked additional sequence elements required for promoter activity in the seed cells. As indicated in the brief (bottom of page 18), substantial utility means that "one skilled in the art can use a claimed discovery in a manner which provides some *immediate* benefit to the public", *Nelson v. Bowler*, 206 USPQ2d 881, 883 (CCPA 1980) (emphasis added). Since the specification does not describe the corresponding promoter, or any other specific nucleic acid molecule, sufficient to inform one skilled in the art

that it has been isolated, there can be no "*immediate* benefit to the public" in using the claimed nucleic acid molecule in this capacity; "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion", *Brenner v. Manson,* 148 USPQ 689 (US 1966) at page 696.

Applicants assert that the Board compared the disclosed utilities to that of a paperweight. The decision of the Board (page 26) discusses using ibuprofen in a jar as a paperweight as an illustration that not all utilities are specific. This was not presented as an analogy to the general utilities disclosed in the specification. An invention does not meet §101 unless and until it is refined and developed to this point-where specific benefit exists in currently available form, *Brenner* at 695. In the instant case, the claimed nucleic acid molecules can be used in various methods to generate information, e.g. whether the *G. max* genome comprises a polymorphism that can be detected with the claimed nucleic acid molecule. It is the contention of the Office and the Board that the instant invention has not been refined and developed to this point-where specific benefit exists in currently available form; that at the time the invention was made, its only use was to gain more information about nucleic acid molecules embraced by the claims and to then identify a substantial use for the nucleic acid molecule. Any EST can be used to gain more information about itself or about potential uses it might have. Such exploratory activity provides no specific benefit in currently available form. The fact that the claimed invention has potential to do so after future research on it is not sufficient to meet the requirements of §101, see *Kirk* at pages 52-53.

J) Response to Reply Section 2.B. (pp. 25-28).

Essentially the same arguments were presented in the Brief of 31 Jan. 2001 (Section 8.C.2), and were addressed in the Examiner's Answer of 06 Aug. 2001 (pages 41-44), with the pertinent arguments being repeated below.

The issue here is whether the general disclosure of potential uses for the claimed nucleic acid molecules, without disclosure of the specific details of such use corresponding to the claimed nucleic acid molecules themselves, meets the requirement for a substantial utility, i.e. is there some immediate benefit provided to the public. Applicants argue that the Wiegand Declaration provides proof that the claimed invention is operable for at least two utilities, e.g. "to detect the presence or absence of a polymorphism". In *Kirk*, the court was not persuaded by *ex post facto* evidence that the claimed invention was useful under §101 because the specifics of that use were not disclosed in the specification. As in *Kirk* (page 53), the Wiegand Declaration here is an attempt "to add statements of usefulness to the disclosure of the application as filed", and as such is "irrelevant to the issue of adequacy of the original disclosure". For example, the original specification does not even mention a use for the claimed invention in detecting sequence variation between *G. max* and *G. soja*, for breeding or any other purpose, nor does it describe the nature of the sequence variation to detect. That Wiegand Declaration was required to introduce such a use, and to supply the details for carrying out that use, shows that the claimed invention could not have provided "some *immediate* benefit provided to the public." First, research on the claimed invention itself was required, to determine whether it did have such a use, and, if so, how to use it, e.g. hybridize to an *Eco*RI chromosomal digest rather than to a *Hin*dIII digest, or any one of the fifteen other enzymes that were not found useful, Wiegand Decl. ¶ 22 and Exhibit C. Also, as noted by the Board (Decision, page 24) the Wiegand

declaration (¶ 20-23) does not indicate whether or how the reported results provide any significant knowledge, and found that this particular use did not represent a "substantial" utility.

This situation is not analogous to that in *Nelson* where the original *specification* (not an *ex post facto* affidavit) disclosed very specific pharmacological activities for the claimed compounds that the court deemed an adequate showing of practical utility. The court specifically contrasted the situation with that in *Rey-Bellet v. Englehardt*, 181 USPQ 453, (CCPA 1974) where the disclosed evidence for pharmacological activity was deemed inconclusive, and thus failed to prove practical utility. In both cases, the claimed compounds were structural analogs for prior art pharmacologic compounds with known specific uses. The utility issue turned on whether evidence disclosed in the specification was sufficient to establish pharmacological similarity as well. That is not the case here: the original specification does not disclose any specific use for the claimed nucleic acid molecules other than using them to identify one, much less a known structural analog with a known specific use to which the claimed nucleic acid molecules can be compared. For example, the specification discloses that one potential use of an EST is to detect a polymorphism that is linked to a desired or undesired trait. However, the specification does not disclose that a polymorphism even exists in *G. max* (much less in *G. soja*) that can be detected with the invention, or that the hypothetical polymorphism is linked to a desired or undesired trait, much less what that trait is.

With respect to the "real world" value of ESTs in general, it is asserted that there is "no question that the public has recognized the benefits provided by the claimed subject matter, and has attributed "real world" values to such nucleic acid molecules". It is unclear as to what evidence Applicants are alluding. The evidence supplied by Applicants shows that a

multimillion dollar industry has arisen surrounding buying and selling EST databases and clones, not that anyone in this industry has bought or sold the claimed subject matter. More importantly, however, footnote 18 of the Brief filed 31 Jan. 2001 acknowledges that simply because a product, such as an EST sequence database or clone library, is bought and sold does not mean it has patentable utility. The footnote goes on to state that buying and selling ESTs is evidence that ESTs are "related to the world of commerce". However, that a product is "related to the world of commerce," because it is bought or sold, does not mean that the product has patentable utility. Evidence that ESTs are bought and sold, or that ESTs are "related to the world of commerce" because they are bought and sold does not identify a specific and substantial patentable utility. The evidence provided by Applicants in this regard does not establish any nexus between the commercial value of ESTs, in general, and specific and substantial utility under §101 of uncharacterized ESTs in general or the claimed subject matter in particular.

Applicants compare processes using ESTs to "industrial product[s] used in an industrial process" such as fermentation. This analogy is not persuasive. At least in fermentation, one has an idea of what one is making, e.g. beer or a specific recombinant protein. The specification does not describe any specific and substantial use for the claimed nucleic acid molecules in the capacity of making some other useful compound, because it describes no specific compound and no specific and substantial use for the compound made, e.g. the corresponding protein or mRNA. As the reply (at page 8, 1st full para.) states:

> It is irrelevant whether the corresponding mRNA or polypeptide themselves have utility because Applicants are not relying on utility of the mRNA or polypeptide to establish utility of the claimed nucleic acid molecules.

Applicants take issue with the statement in the Board's decision at page 30 and repeated in the preceding Office action at pages 18-19, in summary that simply because a collection of nucleic acid molecules, such as on a microarray, may have specific and substantial utility in assessing gene expression does not mean that each specific nucleic acid molecule on that array would have specific and substantial utility. Applicants' reply here ignores the preceding explanation on pages 28-29 of the Board Decision. In essence, the instant specification does not disclose any information that would allow one to determine what the data point showing expression of gene corresponding to SEQ ID NO: 1 would mean, or how the information provided by this data point would be useful in any practical way. Rather the specification leaves it to one of skill in the art to engage in experimentation to determine the meaning or practical use for this data point. In the absence of such information, the presence of the claimed nucleic acid molecule makes no contribution to the utility or usefulness of the microarray. Its presence would be no more useful in assessing the meaning or practical use of the gene expression results for the microarray as a whole than would be the presence of the manufacturer's label on the microarray.

K) Response to Reply Section 2.C. (pp. 28-31).

Applicants insist that the Office is challenging the credibility of the general and vague utilities asserted in the specification. To reiterate, the credibility of the assertions has not been addressed in the rejection because of the absence of an asserted specific and substantial utility or evidence of a well established utility for the claimed invention at the time the application was filed. The Office acknowledges – again - that the claimed nucleic acid molecule would hybridize to genomic DNA and mRNA from *G. max*. However, the Office holds that the specification does not disclose a specific and substantial utility for doing so.

The Office acknowledges that IF a restriction fragment length polymorphism exists in the genome of *G. max*, THEN the claimed invention could be used to detect it. However, the specification does not disclose existence of such a polymorphism or its identity. Contrary to Applicants' repeated assertions, the Wiegand declaration does not show the existence of a "polymorphism", i.e. variation between *G. max* individuals, that can be detected with the claimed invention. The showing of sequence differences between two different species, *G. max* and *G. soja* (see Ahmad for example), and referring to such differences as polymorphisms, is not consistent with the specification (page 28). See Section E above for further explanation.

The Office acknowledges that IF a practical use is developed in the future for determining the level of mRNA corresponding to SEQ ID NO: 1, THEN the claimed invention could be used to measure such level. However, the specification does not disclose how the results of such measurement would provide any information of practical significance. Thus, the specification does not provide a specific and substantial utility for measuring the level of mRNA to which the claimed nucleic acid molecule would hybridize. See Section C above for further explanation.

With respect to Foster-Hartnett and Liebhard, Applicants state they "are not relying on these references to establish utility of the claimed nucleic acid molecules," but to show that the use of molecular markers is an important aspect of genome mapping and identifying significant genes. However, these publications were published well after the application was made, and Applicant has not explained how they show what was well established when the application was made, which is at issue here. Furthermore, in the reply of 06 Oct. 2003, Applicants (page 7) relied upon these references to show that the utility of ESTs was well recognized in the art. The

issue here is not whether molecular markers in general are useful, but whether the claimed invention was useful under §101 when the application was filed. Neither reference demonstrates that hypothetical, uncharacterized molecular markers had well established utility. The instant specification does not disclose that a polymorphism detectable with the claimed invention exists in the *G. max* genome or its identity, and so also does not disclose any molecular marker that the claimed invention could be used to monitor, whether as part of genetic mapping or as a marker linked to a trait of practical interest. Using the claimed invention to determine whether such a polymorphism or marker exists, and, if so, then determining whether it can be used to monitor a trait of practical interest amounts to characterization of the claimed invention and its possible practical uses. Such use does not meet the statutory utility requirement, *Brenner* at 696.

L) Response to Reply Section 3 and its subsections. (pp. 31-43).

Essentially the same arguments were presented in the Brief of 31 Jan. 2001 (Section 8.D. .2; 8.D.2.a; & 8.D.2.b), and were addressed in the Examiner's Answer of 06 Aug. 2001 (pages 45-53), with the pertinent arguments being repeated below. The reply in section 3.A. is directed to the rejection for lack of utility and adds no new points of argument. The arguments in traverse of the rejection for lack of utility have been addressed above.

To summarize the additional grounds of rejection, the scope of claim 1 is astronomically huge, when one only considers additional nucleic acid sequences added to SEQ ID NO: 1. While the claims do embrace nucleic acid molecules with predictable hybridization performance characteristics under certain well-controlled conditions, whether as a probe or a primer, the claims are not limited to such nucleic acid molecules, nor do the claims include any functional limitations or intended use limitations restricting their utility to one involving hybridization, or

any other function. The claims embrace many embodiments that would simply not function appropriately in hybridization (no hybridization or hybridization to non-target nucleic acid molecules), and the specification does not teach how to use the large number of embodiments that are inoperative for hybridization. This is not simply a situation where the claims embrace few inoperative embodiments (relative to the scope of the claim) in one disclosed use, e.g. hybridization.

For example, the Wiegand Declaration (at ¶ 13) states that one skilled in the art would know that addition of soybean sequences to SEQ ID NO: 1 would prevent efficient use of such a combined sequence as a hybridization probe for soybean nucleic acid molecules. However, this presupposes that one would know *a priori* whether any arbitrarily chosen nucleic acid sequence was or was not soybean nucleic acid or would or would not cross-hybridize with other soybean nucleic acid molecules. Such nucleic acid molecules are embraced by the claims.

The Examiner agrees with Applicants that the claims may include inoperative embodiments; however, only if the operative embodiments can be identified without resort to undue experimentation, and the claimed subject matter bears a reasonable correspondence with the enabled embodiments. See e.g. *In re Vaeck*, 20 USPQ2d 1438, 1444-1445, where the affirmance of the rejection of the broad claims was largely due to unpredictability. In *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (CA FC 1984), the court qualified the statement:

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude * * * possible inoperative substances * * * *"

with the statement:

> Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid.

It is the latter situation at issue here.

The Examiner agrees with Appellant that lack of absolute predictability does not preclude enablement or that the requirement for "some experimentation ... does not preclude enablement", but holds that the wholesale "make-and test" experimentation required here to enable the full scope of the claims was not what the courts had in mind. In *Atlas Powder*, the specification in question contained ample guidance for the substituents in the claimed combinations. In contrast, the instant specification contains little guidance on the nature of additional sequences that might be attached to the sequence of SEQ ID NO: 1 for use in hybridization or any other methodology. It is acknowledged that those of skill in the art were aware of various nucleic acids that could be conventionally attached to a probe without adversely affecting its performance characteristics in hybridization, such as a vector backbone or oligonucleotides such as linkers, adapters, or PCR heels (see Wiegand Declaration at ¶ 13). However, the claims are not limited to nucleic acid molecules further comprising such nucleic acids. The claims embrace adding to SEQ ID NO: 1 any additional nucleic acid, of any length or sequence, regardless of purpose. Adding nucleic acids of arbitrary length and sequence to a probe sequence, such as SEQ ID NO: 1, is *not* conventional in the art. There must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed, see *Vaeck* at page 1445. The specification does not teach which unconventional additional sequences would be consonant with using the claimed nucleic acid

molecules in hybridization, nor does it teach how to use those claimed nucleic acid molecules that are unsuitable for hybridization.

The relevance of the "benzpyran" example (brief, page 30), which appears to be hypothetical, to the instant case is unclear. Nucleic acid molecules are not analogous to many types of product, such as benzpyrans. Those in the art employ nucleic acid molecules for many different uses, and these molecules are in heteropolymeric chains of a wide variety of different residue sequences and sizes, from oligonucleotides a few residues in length up to chromosomes of 1,000,000 or many more residues in length. Not all of these are suitable for uses requiring hybridization, nor would those skilled in the art even consider doing so.

Although the level of skill in the hybridization art is high and that the prior art provides ample general guidance on hybridization, the art also recognizes that choosing specific probes for a specific application must be taken on a case-by-case basis. The only explicit guidance in the specification with regard to a probe is SEQ ID NO: 1 itself. The only generally disclosed target nucleic acids disclosed are SEQ ID NO: 1 and the corresponding mRNA and genomic DNA from soybean and perhaps from other plants. Given this limited disclosure, it is unclear how one skilled in the art would use the vast majority of nucleic acid molecules embraced by the claims, which includes a nucleic acid molecule comprising SEQ ID NO: 1, 469 nucleotides long, attached to 1,000,000 nucleotides, or greatly more, of arbitrary sequence.

Applicants urge the concerns that the claims embrace inoperative embodiments are irrelevant, citing *Atlas Powders* and *Ex parte Cole*, 223 USPQ 94, 95 (BPAI 1983). However, *Atlas Powders* stated that if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed

invention, the claims might indeed be invalid. *Cole* is inapposite because the instant rejection is not based upon any argument that each embodiment be useful for each and every use. Only one use, hybridization, is at issue since the specification does not disclose any other use that does not require hybridization at some point. Furthermore, the claims in *Cole* each contained functional limitations or intended use limitations in addition to structural limitations. The instant claims have no functional or intended use limitations that would implicitly place relevant structural limitations on the claimed nucleic acid molecules.

Pages 38-43 summarize pertinent case law with respect to enablement and prior art references which show the state of the prior art and the skill of one in the pertinent art. Since the only working example shows using a claimed nucleic acid molecule, a *conventional* plasmid clone, as a template for PCR amplification, the second and third *Wands* factors do not appear to be met in this case. What is missing from the specification, and the general knowledge in the art, is guidance on the nature of additional nucleic acid added to SEQ ID NO: 1 for uses requiring hybridization.

While it is true that a considerable amount of experimentation is permissible if it is routine, i.e. typically performed by those in the pertinent art, that is not the situation here. The issue is not whether it is routine to try different hybridization protocols in order to optimize (see Wiegand Declaration, ¶ 11). The question is whether it is routine in the art to add arbitrary nucleic acid, of any length or sequence, to a defined probe sequence, e.g. nucleic acid molecule consisting of SEQ ID NO: 1, and whether it is routine to then test such complex probes for operability. The sheer magnitude of the embodiments claimed, i.e. infinite, is evidence that such an undertaking would be extremely laborious and lengthy. The problem here is that the claims

embrace far more than would be conventionally employed for uses requiring hybridization. The court in *Atlas Powders* stated that "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid". That is the situation here. Claim 1 places no physical or functional (use) limitations on the additions to SEQ ID NO: 1, and does not teach how to use those embodiments that cannot be used for hybridization. Given the astronomical number of possible embodiments, the number of embodiments that cannot be used for hybridization is likely to be large.

Applicants have added an analogy to their arguments comparing the claimed invention to a claimed carburetor taught for use in a car. Applicants posit that one of skill in the art would immediately recognize that it would not be operable in other types of vehicle, and if designed for a Ford, that extensive modification would be required to use it in a Porsche. Applicant concludes that these restrictions would not invalidate a claim directed to a carburetor comprising additional elements. However, this analogy is not applicable here. By naming the claimed product a carburetor, the function or intended use of the device is clearly indicated, and would imply certain structural limitations consistent with that use. The instant claims include no limitation of intended use or function that would imply structural limitations. Since one of skill would be aware that the claimed carburetor would not function in various vehicles, and if designed expressly for a Ford, and not other cars, one presumes that the claims included structural limitations as well upon which such a conclusion would have been based. Also, the mechanical arts are considered to be highly predictable. One in this art can immediately recognize from the claim what vehicles the claimed carburetor would be operable in because of this predictability

and also because one knows the structure of the carburetor and the engines of the various vehicles. In contrast, there is no evidence of record that one of skill in soybean molecular biology had known the structure of the soybean genomic DNA, nor could one have predicted its structure. Consequently, one cannot immediately recognize whether an arbitrary additional sequence added to SEQ ID NO: 1 would permit the nucleic acid molecule to be used in hybridization against the soybean genome, e.g. it hybridizes with genomic sequence other than that to which SEQ ID NO: 1 would hybridize, as in Wiegand declaration at ¶ 13. One would expect that claim 1 embraces a substantial number of embodiments that are inoperative (or of no use) for hybridization to soybean genomic DNA, and the specification does not teach how to use them.

M) Response to Reply Section 4 and its subsections. (pp. 43-47).

Essentially the same arguments were presented in the Brief of 31 Jan. 2001 (Section 8.E; 8.E.1; & 8.E.2.), and were addressed in the Examiner's Answer of 06 Aug. 2001 (pages 53-56), with the pertinent arguments being repeated below.

The issue is whether Applicants were in possession of the genus being claimed (claim 1). This genus is not restricted to any particular disclosed subgenus or species, such as vectors comprising SEQ ID NO: 1 as an insert. The only nucleic acid molecules described by complete structure are the one consisting of SEQ ID NO: 1. The only nucleic acid molecules comprising SEQ ID NO: 1 described in the specification by other characteristics are vectors comprising SEQ ID NO: 1 in general, and one species LIB3049-003-Q1-E1-H7 (ATCC PTA-2416), which comprises pSPORT, SEQ ID NO: 1, and some additional unspecified nucleotides. While it is acknowledged that Applicants need not describe "every nuance" of the claimed invention, the

written description must bear a reasonable correlation to that which is claimed. The disclosed subgenus and species embraced by the claims are not representative of the entire genus being claimed. The genus of nucleic acid molecules being claimed embraces any and every type of nucleic acid molecule that comprises SEQ ID NO: 1 and additional sequences of any size and sequence, not just vector backbones. Clearly, at the time of filing, Applicants were not in possession of complete mRNA or genomic materials that contain the common EST fragment (SEQ ID NO: 1), which are embraced by open-ended claim 1. The specification does not disclose what characteristics these additional sequences may or may not have that are consistent with the operability of the nucleic acid molecules as probes or primers for detection of SEQ ID NO: 1 in a target sequence, and all disclosed uses for the claimed nucleic acid molecules are fundamentally as probes or primers, at least in some aspect.

With respect to full length mRNAs, cDNAs and genomic sequences, one skilled in the art would reasonably conclude that the claims embrace these nucleic acid molecules, and the specification provides no physical (i.e. structural) characteristics of these molecules to distinguish them from other nucleic acid molecules comprising SEQ ID NO: 1 and no other indication that would suggest Applicants possessed them. This particular subgenus embraced by the claims has a disclosed potential utility not possessed by those members of the claimed genus useful only in hybridization. Full length mRNAs, cDNAs and genomic sequences (genes) would encode the corresponding protein(s).

A fundamental issue here is specific to the very narrow class of product that is nucleic acid molecules. The basic question upon which Applicants and the Office disagree is whether the disclosure of a partial sequence (SEQ ID NO: 1) of otherwise uncharacterized nucleic acid

molecules that may encode a corresponding protein is sufficient to establish possession of a broad genus based solely on the description of the partial sequence, where the broad genus embraces the uncharacterized nucleic acid molecules by default. The subgenus of uncharacterized nucleic acid molecules that encode any corresponding protein is explicitly alluded to in the specification, and disclosed as possessing an additional use *not* possessed by any other members of the broad genus being claimed, i.e. encoding the protein. The specification does not provide any structural or functional characteristic for these desired nucleic acid molecules, which encode the protein, that would distinguish them from the other members of the genus, which simply comprise SEQ ID NO: 1 as the sole distinguishing feature. As stated in *University of California v. Eli Lilly and Co.* at page 1404:

> An adequate written description of a DNA ... "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

That Applicants claims embrace nucleic acid molecules that encode a corresponding protein, whatever it may be, is clearly evident from the specification and the reply (page 47). The court in *University of California v. Eli Lilly and Co.*, at page 1405, further noted regarding generic claims:

> A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe* , 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . .").

In the instant case, the only species specifically enumerated are the nucleic acid molecule of SEQ ID NO: 1 itself and the specific deposited clone from which it was isolated. The specific embodiments that include nucleic acids in addition to SEQ ID NO: 1 that will allow the corresponding protein to be encoded cannot be predicted without the coding sequence itself. This coding sequence has not been disclosed. Clearly, the specification would not show one skilled in the art that these desired subcombinations were possessed by Applicant, and thus the embracing genus was also not possessed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

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